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EDITORIAL

ARE GENERICS TRULY EQUIVALENT?

THE question posed by the title of this editorial is one which is answered in the affirmative all too glibly these days. Well informed pharmacists have struggled with this question for many years and, indeed, it is one which requires many day to day decisions if the pharmacist is to discharge his full professional responsibilities, with patient health and welfare given top priority in passing judgment.

Some of the widespread publicity given the question of generic equivalents which has stemmed from the Kefauver hearings has led far too many, both in and out of the professions, to grossly oversimplify the complexities which this question really poses when one approaches it scientifically and with all information available on the subject. In all likelihood, the most common error made is the assumption that, if one places in a dosage form a given amount of some medicinal substance, this dosage unit will produce the full effect of the drug contained regardless of by whom it is made, by whom it is taken, and when. Nothing could be further from the truth. It would be well for us to examine some of the variables which are attached to this problem. In the first place, the fact that a given amount of some drug is placed in a dosage form is no guarantee at all that this drug is available in full amount to exert its therapeutic effect. The tablet, capsule, or solution in which the drug is contained may, upon analysis, show that the full amount is present but the technique involved in analysis—particularly in a solid dosage form—involves methods of extraction having no relationship at all to the physiologic conditions met in the gastrointestinal tract. A tablet, for example, may be extracted with acetone or ether to remove the active principle but it is a rare human stomach or intestine indeed in which such solvents are found! As every scientist working in pharmaceutical research and development knows, to be effective, a tablet must not only disintegrate but it must release the drug from the primary granules making up the tablet and do so before they have passed too far along the gastrointestinal tract to make absorption possible. In

the case of sustained-release products the technology involved must be even more delicately balanced since no two drugs can be prepared in exactly the same way if a satisfactory sustained-release action is to be achieved.

A fully effective dosage form also involves long, drawn-out stability studies to make sure that a year or two years after the product is marketed it will still contain the labelled amount of active ingredient and in a form still available for proper absorption. While the Food and Drug Administration presumably has the responsibility of seeing this is so, it is obviously impossible to test every batch of every product made. Drug certification would not solve this problem either since by no stretch of the imagination could every batch of every drug product made in the U. S. be subjected to such scrutiny without a paralyzing bureaucracy and doubling the cost of medical care. It is for this reason that the Food and Drug Administration checks most closely on samples of drugs distributed by companies known to cut corners and to be satisfied with somewhat less than the highest standards.

Many other aspects relating to quality are likewise involved. No parenteral product, for example, can have its sterility known for a certainty unless every package of every lot is examined for sterility. If this were done, none would be left for sale. While proper sampling gives reasonable assurance of good quality control, there is a considerable variation in company standards as to what constitutes a representative sample. Dozens of other examples of the vicissitudes of pharmaceutical manufacturing could also be given.

Those who contend that generic equivalents are truly equivalent are saying that there is no such thing as pharmaceutical technology and they are subscribing to the belief that the thousands of pharmaceutical scientists and technologists who devote their time and talent to the development, production, and control of the world's finest pharmaceuticals are, in essence, accomplishing nothing. The truth is just the opposite. Modern pharmaceutical technology is just as highly specialized as nuclear physics, space technology, or any of the other more glamorous fields with which the public and the government are presently enchanted.

The practicing pharmacist, even though he knows this full well, is still somewhat hard pressed in judging whether some generic equivalent or some other brand of a given product may reasonably be

expected to accomplish the same therapeutic result. While he might perform certain laboratory tests to give fairly valid evidence that such was the case or not, generally he cannot afford the time and effort to do this. His decision must usually be based upon his personal knowledge and experience regarding the products of the company in question and based also upon its long-term reputation in supplying the finest quality medicinals. A practicing pharmacist who places his professional integrity above all else would satisfy himself on this score first and consider the cost aspect of the medication in a secondary role where it belongs. This, he does routinely in selecting drugs for use by himself and his family. Professional integrity would not permit him to do other than this for those who place their trust in him as their pharmacist.

We repeat the question: Are generics truly equivalent? The answer is: They may be. But the answer is surely not easy to come by and it cannot be dictated on the basis of cost alone. It is for this reason that pharmacists and physicians alike must resist all those efforts to so define them by government edict or regulation. The quality of medical care is something which the professions have as their responsibility and no abrogation of this responsibility should be permitted, regardless of its source.

L. F. Tice

A QUALITATIVE AND QUANTITATIVE INFRARED STUDY OF BINARY MIXTURES OF PURE ADRENOCORTICAL STEROIDS [1]

By William H. Parsons,[2] Alfonso R. Gennaro,[3] and Arthur Osol [3]

THE method now most generally used for the study of powdered samples in the infrared region is the compressed alkali-halide disk technique proposed by Schiedt and Reinwein (1) in 1952. The method has wide utility both for qualitative and quantitative analyses, but also has certain limitations (2-10). Noteworthy among the advantages possessed by the procedure is the relative freedom from background absorption. Unless grinding time is excessive (more than five minutes in a mechanical grinder), there is little chance of interaction between the alkali-halide and the absorbing sample for most organic compounds; the possibility of interaction is much more prevalent in techniques utilizing solvents as mulling agents. With improvements in the design of dies and of collimating devices, it is now possible to perform a quantitative infrared analysis in which quantities of sample of the order of fractions of a milligram may be readily detected (3).

Photometry, however, usually limits the precision of infrared analyses of multicomponent mixtures. The response of infrared detectors is linear with transmittance but logarithmic with absorbance, which is proportional to the concentration of the infrared absorbing components. The constant error in measurement of transmittance corresponds to an absorbance error which increases with absorbance. Thus, the higher the measured absorbance, the higher the absolute error in the measurement of concentration. This relationship seems to impose an upper limit on the precision of spectrophotometric determinations.

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[1] This paper is abstracted, in part, from the thesis of W. H. Parsons submitted to the Graduate School of the Philadelphia College of Pharmacy and Science in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June 1960.

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Differential spectrophotometry (11) raises this upper limit. In this technique, a sample is precisely matched against a standard, permitting absorbance to be measured within about 0.002 unit over a wide range (12). Both beams of a double-beam spectrophotometer are used; the sample is placed in the sample beam and the standard in the reference beam, enabling the instrument to sense the ratio of the radiant energy of the sample to that of the standard.

Essentially, the analytical problems to which differential analysis can be applied may be divided into two categories:

1. Those which require the determination of impurities present in small concentration ranges.

2. Those which require accuracy of determination of a component in a given concentration range (this does not necessarily have to be a low concentration range of the component to be determined).

The sole difference between the two types of problems is that, in one case, the sample to be analyzed is compared with the major component alone; whereas, in the second case, comparison is made with a mixture containing the lowest expected concentration of the component to be measured. For example: If "A" is to be determined in "B", and if it is known that "A" will always be in the region of 70 to 80 per cent, then a mixture containing 70 per cent "B" should be used for comparison rather than "B" alone (13).

The latter method is applied in this study to the determination of small amounts of a known impurity in a "pure" material. In this technique, applied where there is overlapping of absorption bands of major and minor components, the absorption due to the major component is essentially subtracted from the total absorption. The remaining absorption is due to the minor component (14). If, however, some of the "impurity" (minor component) to be measured—for example, 1 per cent—is present in the material to be used as standard, all determinations based on this standard will be 1 per cent lower than the true value. The accuracy is thus dependent upon the availability of a standard sample free of the impurity to be measured. Since standard steroids of the required degree of purity are not available, excess solute separated in the course of a series of phase solubility analyses was utilized for this purpose (15).

The combination of the technique of phase solubility analysis with infrared differential analysis utilizing the alkali-halide compressed disk as the dispersing medium is undertaken in this study with the thought that the increased sensitivity, specificity, and freedom from solvent-sample interaction as well as solvent absorption might minimize problems of purification and possible spectrophotometric insensitivity.

Experimental

The experiments performed were both qualitative and quantitative. The qualitative part consisted in obtaining infrared spectra of the nine steroids in solution, in heavy liquid petrolatum mulls and in potassium bromide disks. All observations were made using a Beckman IR-4 infrared spectrophotometer, equipped with sodium chloride prisms, operated as a double-beam instrument. Solution cells were of the fixed-thickness type using sodium chloride optics. Cell thicknesses were determined by interference methods and window flatness was assured using the "Newton's rings" technique. Copper (rather than lead) spacers were amalgamated between front and back windows. Table I lists the solvents in which saturated solutions were prepared, along with cell thickness.

Mulls were prepared by placing 3.0 mg. of the appropriate steroid and three drops of U. S. P. mineral oil (heavy) on one grinding surface of a mulling device consisting of two glass cylinders, each one inch in height and one inch in diameter. The grinding surface of the sec-

TABLE I

Steroid	*Solvent*	*Cell Thickness (mm.)*
Cortisone	Bromoform	1.0
Hydrocortisone	Carbon disulfide	1.0
Prednisone	Bromoform	1.0
Prednisolone	Bromoform	1.0
Cortisone Acetate	Bromoform	0.09
Hydrocortisone Acetate	Bromoform	1.0
Prednisone Acetate	Bromoform	0.09
Prednisolone Acetate	Bromoform	1.0
Hydrocortisone Succinic Acid	Bromoform	1.0

ond cylinder was placed on top of the first, and mulling was continued until a translucent semi-liquid was attained. This was placed between sodium chloride plates and the spectra run.

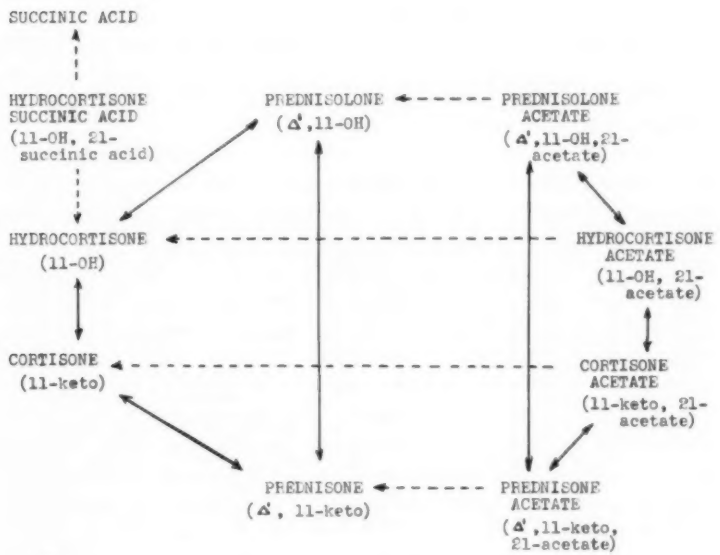
Potassium bromide disks were prepared using reagent grade KBr which had been previously ground and dried for eight hours in an oven at 140°C., and cooled to room temperature in a desiccator. The required amount (5.00 mg.) of the appropriate steroid was determined on a SEKO semi-micro balance. To this was added sufficient KBr to make 500.00 mg. The steroid and KBr were transferred quantitatively to the stainless steel capsule of a mechanical grinder and ground for 3.0 minutes. Exactly 250.00 mg. of the finely comminuted material was then transferred quantitatively into the chamber of a KBr die, model MK-3 manufactured by Research and Industrial Instruments Co. of London, England. The die was assembled, placed in a press and a vacuum pump attached. A gauge pressure of 1000 pounds was gradually applied while the die was partially evacuated; with the vacuum pump in position, the pressure was gradually raised to 5000 pounds per square inch and maintained for five minutes. The pressure was gradually released, the die disassembled, the clear disk removed, stored for one hour in an oven at 40°C., and placed in a suitable sample holder to be inserted in the sample beam of the spectrophotometer. A 250.00-mg. compressed KBr blank was placed in the reference beam to offset any background effects of the KBr in the sample beam. These conditions of preparation produce a 250.00-mg. transparent disk 1.50 cm. in diameter, 0.50 $\pm$ 0.01 mm. in thickness and having a steroid concentration of 1.00 per cent.

The quantitative determinations undertaken in this study involve differential infrared spectrophotometery of those steroid pairs that are structurally most closely related of the group of steroids chosen. Twenty-two interdeterminations of synthetic binary mixtures of the steroids were investigated. The interdeterminations and the structural differences among the steroids studied are diagrammed in Figure 1. These pairs of compounds were chosen since they are chemically very similar and because they constitute possible chemical contaminants in each other's presence due to the sequence of steps followed in their syntheses.

In the procedure for infrared differential analysis of the mixtures, there was placed in the sample beam of the spectrophotometer a compressed disk containing 1.00 per cent of a steroid dispersed with

varying amounts of a second steroid in sufficient KBr to make a total mass of 250.00 mg. This combination constituted the synthetic "impure" sample. In the reference beam was placed a compressed disk containing 1.00 per cent of the first steroid dispersed in sufficient KBr to make a total mass of 250.00 mg. This constituted the "pure" reference disk.

To minimize non-spectrophotometric errors and to provide a suitable range of synthetic impure samples, two triturations of each steroid in KBr were prepared. One of these (T) was made by adding to 50.00 mg. of the appropriate steroid (S_1) sufficient KBr to make 500.00 mg.; this was ground for 3.0 minutes, immediately transferred to a vial, and stored in a desiccator. The second trituration was



Key

⟷ Indicates each substance determined as a minor component in the presence of the other.

- - - - → Indicates the single substance determined as a minor component in the presence of the other.

( ) Indicates distinguishing structural characteristics.

FIGURE 1

prepared in two steps: (1) 25.00 mg. of the appropriate steroid (S_2) and sufficient KBr to make 500.00 mg. was ground for 3.0 minutes; (2) a 25.00-mg. portion of this mixture was ground with sufficient KBr to make 500.00 mg.. This last trituration (T′) represents 0.25 per cent of S_2 while T contains 10 per cent of S_1.

To prepare "pure" disks containing 1.00 per cent of S_1, 50.00 mg. of T was added to sufficient KBr to make 500.00 mg.; this was ground for 3.0 minutes and 250.00 mg. of this dispersion was pressed in the die in the same manner as the disks were made for the qualitative spectra.

The synthetic "impure" disks were prepared by taking 50.00 mg. of T and varying amounts of T′, finally adding sufficient KBr to making 500.00 mg. This was ground and dispersed for 3.0 minutes, and 250.00 mg. of the mixture was pressed in the die.

Impurity concentrations were calculated as percentages in the following manner: $\frac{\text{mg. of } S_2}{\text{mg. of } S_2 + 2.50} \times 100\% =$ per cent of S_2 (the synthetic impurity). The figure "2.50" represents the number of milligrams of S_1 in each disk.

To select the most useful wavelength for determining the degree of synthetic impurity, a disk containing 1.00 per cent of S_1 plus an amount of impurity corresponding to approximately 1 per cent of the S_1 concentration was placed in the sample beam. With the spectrophotometer in double-beam operation, the differential "spectrum" was scanned from thirteen microns to five microns. The positions of the two or three deepest bands that appeared were considered as being possible analytical wavelengths. At least three more disks, containing progressively smaller amounts of impurity, were scanned over the same range of wavelengths; the process was repeated with diminishing amounts of impurity in the sample beam until the band selected for analytical evaluation was no longer clearly distinguishable from background. In certain cases, the concentration of impurity had to be in excess of 1 per cent of the total steroid concentration since it could not be certainly determined that the band chosen would yield the desired information at this level of impurity. Thus, to determine hydrocortisone as an impurity in prednisolone, it was necessary to prepare the first "impure" disk containing hydrocortisone in a concentration equivalent to 7.39 per cent of the total steroid present. The process of impurity reduction could be continued only until the

hydrocortisone concentration reached 2.49 per cent, which is the lower limit of detectability of hydrocortisone in cortisone. In every other combination, however, the minimum of synthetic impurity detectable was below 1 per cent.

No attempt was made in this study to analyze the many types of errors that are to be expected in spectrophotometric determinations; Robinson (2, 11) has described the more important of these in detail. However, to compare the precision of all values obtained in a determination, as well as to correlate values between determinations, the following steps were taken for each:

1. A plot of percentage transmission (at the analytical wavelength) vs. concentration of impurity was made.

2. A plot of absorbance ($2 - \log_{10} \%T$) vs. concentration of impurity was made.

3. For each impurity concentration, the standard deviation of five scans of the band depth was estimated.

4. For each of the above impurity concentrations, the coefficient of variation * was estimated.

Results and Discussion

Investigation of these steroidal phase solubility residues in solution, in mull, and in KBr disk shows clearly that background interference is least when the sample is investigated in compressed KBr disk form. Mulls and solutions possess inherent limitations since the mulling agent or solvent is never transparent over the whole range from two to fifteen microns.

For many of the steroids studied, chloroform is a solvent superior to carbon disulfide or bromoform, but it absorbs strongly in the 8-micron region. Since the regions of the spectrum of principal interest include the C=O stretching region (5.3 to 6.3 microns) and the C—O stretching region (7.5 to 11 microns), bromoform or carbon disulfide was used.

The mulling agent used was Liquid Petrolatum U. S. P., which has characteristic absorption bands at 3.4, 6.8, and 7.2 microns which

* The coefficient of variation is defined as $100s/\bar{X}$, where s represents the standard deviation, and $\bar{X}$ the mean of the band depths of five scans of the same band.

showed on the spectra since nothing was placed in the reference beam when the mulls were run.

Compressed KBr disks are virtually free of background if the KBr is of reagent grade and properly dried, and if it is properly ground. Overgrinding can cause absorption in the 9-micron region (7), while undergrinding is known to cause interference fringes, particularly in the 6-micron region.

It was noted that the physical appearance of compressed KBr disks changes rapidly upon their removal from the die. They become clouded, apparently from absorption of atmospheric moisture, with subsequent pitting of their surfaces. This change exerts a marked effect on the character of the infrared spectra. Slight changes in the optical quality of a disk will have an even more accentuated effect when the differential technique is used. The degree of clouding was most pronounced during the first fifteen to thirty minutes that the disk was out of the die.

It was found that these changes could be prevented, and stable disks prepared, by placing freshly made disks in an oven at 40°C. for one hour. Disks processed in this manner seem to undergo an "aging" process and, if properly stored, give reproducible quantitative data even after several weeks of storage.

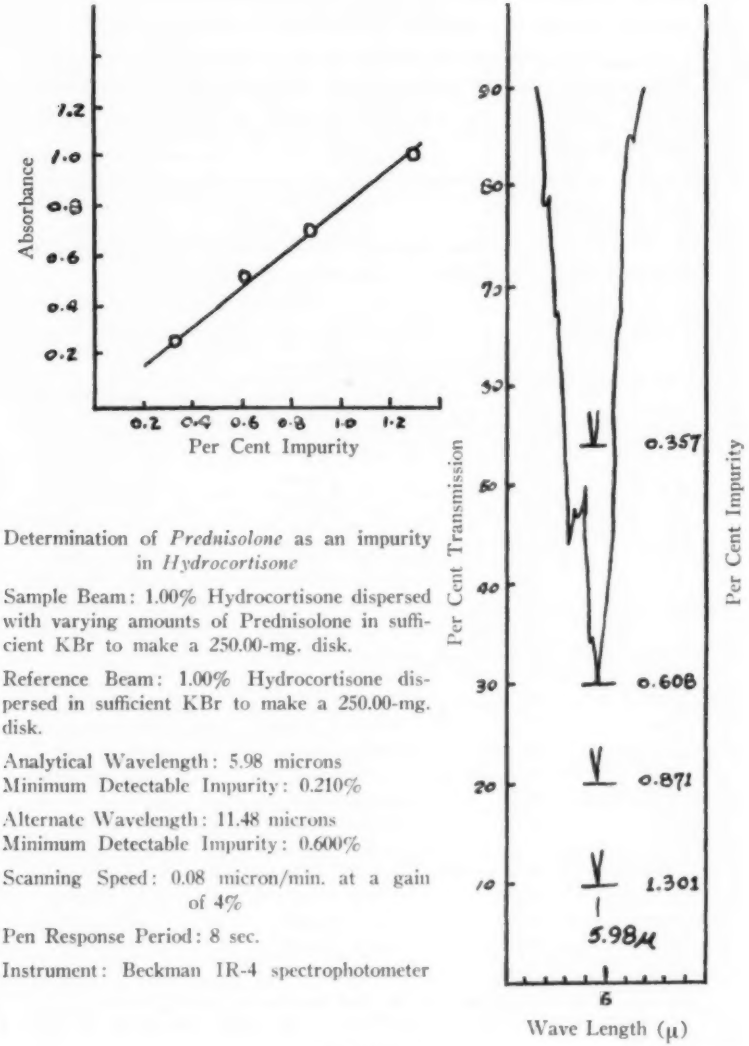
Several investigators (11-14) have noted that the technique of differential spectrophotometry is more sensitive than any other infrared method, particularly when it is desired to determine the concentration of a minor component in a mixture. Wiberley (16) has discussed the theory and use of internal standards in differential spectrophotometry, and further attests to the sensitivity of the method.

Figure 2 illustrates the type of differential curve observed in this study and Table II, the data that pertain to each of the interdeterminations.

Summary

The spectra of nine adrenocortical steroids previously purified by phase solubility analysis were investigated. Any alterations of the spectra of the same compound studied under varying conditions of sample preparation (solution, mull, and KBr dispersion) were noted.

The technique of infrared differential spectrophotometric analysis in compressed KBr disks was found applicable and, therefore, was used for the determination of a minor steroid contaminant in synthetic binary mixture with a chemically similar steroidal major component.



Determination of *Prednisolone* as an impurity in *Hydrocortisone*

Sample Beam: 1.00% Hydrocortisone dispersed with varying amounts of Prednisolone in sufficient KBr to make a 250.00-mg. disk.

Reference Beam: 1.00% Hydrocortisone dispersed in sufficient KBr to make a 250.00-mg. disk.

Analytical Wavelength: 5.98 microns
Minimum Detectable Impurity: 0.210%

Alternate Wavelength: 11.48 microns
Minimum Detectable Impurity: 0.600%

Scanning Speed: 0.08 micron/min. at a gain of 4%

Pen Response Period: 8 sec.

Instrument: Beckman IR-4 spectrophotometer

FIGURE 2

Specificity of the analytical determinations performed on the twenty-two steroid systems investigated was assured by the following:

1. The existence of an absorption maximum at a characteristic wavelength (referred to as the analytical wavelength).

2. The provision, wherever possible, of an alternate analytical wavelength.

3. The distinctive form of the absorption band at the analytical wavelength.

4. The linear variation of absorbance at the analytical wavelength with concentration of the minor component.

TABLE II

STEROID INTERDETERMINATIONS

Major Component	*Minor Component*	*Minimum Detectable Concentration of Minor Component (%)*	*Analytical Wavelength (microns)*
Co	Hy	0.130 (0.514)	6.02 (6.85)
Hy	Co	0.213 (0.599)	5.83 (11.04)
Hy	Pl	0.210 (0.600)	5.98 (11.48)
Pl	Hy	2.490 (3.150)	6.02 (11.55)
Pn	Pl	0.096 (0.700)	5.98 (9.61)
Pl	Pn	0.061 (0.310)	6.00 (11.15)
Pn	Co	0.060 (0.150)	5.80 (6.16)
Co	Pn	0.080 (0.302)	5.81 (11.15)
HSA	Hy	0.201 (0.414)	6.02 (11.15)
HSA	SA	0.210 (0.344)	6.03 (7.64)
PlA	Pl	0.251 (0.251)	6.27 (8.08)
PnA	Pn	0.310 (>5)	5.95 (none)
CoA	Co	0.251 (0.341)	5.94 (7.86)
HyA	Hy	0.412 (>5)	5.80 (none)
PnA	CoA	0.650 (>5)	5.97 (none)
CoA	PnA	0.519 (0.600)	5.94 (5.84)
PlA	HyA	0.501 (0.621)	6.01 (11.15)
HyA	PlA	0.207 (0.470)	6.11 (8.08)
HyA	CoA	0.231 (0.467)	6.10 (5.79)
CoA	HyA	0.491 (0.930)	5.95 (9.48)
PlA	PnA	0.301 (0.410)	6.25 (6.01)
PnA	PlA	0.291 (0.525)	6.17 (5.70)

The figures in parentheses are the alternate usable analytical wavelengths and the minimum detectable concentrations of the minor component at these wavelengths.

KEY: Co = Cortisone; Hy = Hydrocortisone; Pl = Prednisolone; Pn = Prednisone; HSA = Hydrocortisone succinic acid; SA = Succinic acid; PlA = Prednisolone acetate; PnA = Prednisone acetate; CoA = Cortisone acetate; HyA = Hydrocortisone acetate.

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COMBINATION CHEMOTHERAPY IN ACUTE LEUKEMIA IN CHILDHOOD:

Corticosteroids, 6-Mercaptopurine, and Folic Acid Antagonists

By John R. Sampey *

CORTICOSTEROIDS, 6-mercaptopurine (6-MP), and folic acid antagonists have been the most frequently employed chemicals in the management of acute leukemia (35). Some synergistic effects have been noted in combination chemotherapy of these agents in patients of all ages (36, 37). The present study was undertaken to determine from the current literature the action of combinations of these three drugs on acute childhood leukemia.

Corticosteroids Plus 6-Mercaptopurine

Louis and associates (26) reported 19 remissions in 32 children with acute leukemia who were administered a combination of adrenal steroids plus 6-MP; in 23 adults with acute leukemia on the same therapy, there were only five remissions. These results compared with three remissions in five children given 6-MP only, while none of four adults responded to the purine drug alone; and, finally, two adults failed to respond when steroids only were administered, while all three children had remissions to 36 weeks on these hormones. Torres Marty *et al.* (44) administered corticoids first and then 6-MP to 41 children with acute leukemia, and recorded nine complete and 13 partial remissions lasting to 20 months. Tuuteri *et al.* (47) induced 50 per cent survivals for six months in 47 children, with 10 per cent living for 17 months who received 6-MP or folic acid antagonists plus cortisone. In a second publication, Louis *et al.* (25) tabulated 76 per cent remissions in 32 children under 15 years of age and 60 per cent in those over 15 years; only 17 per cent of 29 adults had any response to this combination of drugs.

Schall and Eckler (40) have reported the results on the combination of a variety of agents in 111 children with leukemia during the years 1935-59: they observed no improvement in 25 after the use of transfusions and arsenic preparations; five remissions in 15 chil-

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dren were noted after transfusions, arsenic, sulfonamide, and antibiotic therapy; five in 19 responded to the combination X-rays, urethan, and Sinalost; 16 remissions in 23 children followed treatment with ACTH, cortisone, transfusions, and antibiotics; 24 of 29 improved under alternate hormone and antimetabolite therapy; and, finally, they recorded 16 remissions in 21 children given steroids plus 6-MP. Freireich (17) employed 6-MP to increase steroid induced remissions: of 51 patients between 0 and 20 years of age who experienced a complete remission on corticosteroids, the 28 receiving the purine also had a median survival of 180 days, while the 23 receiving placebo had a median survival of only 60 days. Hrodek *et al.* (23) reported that their best results in treating 36 children with acute leukemia were from the combination corticoids plus 6-MP, followed by the hormones plus aminopterin when resistance developed to the purine antagonist: they recorded 79 per cent remissions and 50 per cent survival for 10 months; in 61 untreated cases, there were no spontaneous remissions and 50 per cent survival for only 2.5 months. Hayashi (20) compared the results in 64 children with acute leukemia who received different chemotherapeutic agents: in 15 administered steroid hormones and 6-MP alone or in combination, he tabulated four clinical and hematologic remissions for an average survival of 4.8 months; in a like number receiving nitrogen mustard or urethan or radiophosphorus or sanamycin, he recorded only two responses for an average of 4.0 months; and, in 34 children given antibiotics and transfusions, he had six remissions, averaging 3.4 months. Carvalho *et al.* (7) employed corticosteroids and antimetabolites, singly or in combination chemotherapy, to induce 19 complete remissions and 14 partial in children under 15 years of age.

Chaptal *et al.* (8,9) released two studies on the treatment of acute lymphoblastosis in children: they secured complete clinical and hematologic remissions for five out of five children, following the use of cortisone plus 6-MP. Hoshino *et al.* (22) described remissions averaging four months in 19 adults and 6.5 months in 16 children who received 6-MP or folic acid antagonist combined with delta cortisone. Moloney *et al.* (29) noted good to excellent remissions in six of eight children with acute lymphocytic leukemia by a combination of steroids and 6-MP; they also found that two of four children with acute myelocytic leukemia had 12 month remissions under this therapy,

while two with acute monocytic had no improvement. Nicolau *et al.* (30) reported five remissions of four to eight months in seven children, following treatment with cortisone plus mercaptopurine. Antonucci and Ramenghi (2) observed a survival of 316 days with the combination of prednisone plus 6-MP in four clinical and three hematologic remissions in five children. Hibino (21) used the combination cortisone, or prednisone, or ACTH with 6-MP to secure remissions in two of five cases. Sato (38) recorded an average survival of only 60 days in children with acute leukemia who received nonspecific therapy, while those on steroids plus 6-MP survived 193 days. In 1959, Bernard *et al.* (3) reported little response in 14 of 20 promyelocytic acute leukemia cases below 20 years of age who were given corticoids plus antimetabolites, although there was one complete remission with delta cortisone plus 6-MP. The next year, Bernard (4) described some good responses in children receiving the combination prednisone plus mercaptopurine. In 1959, Tur (45) described an eight months' complete remission in a child given cortisone plus 6-MP plus transfusions and, the following year, he (46) recommended the combination steroids plus the purine antagonist in children with marked clinical and hematologic symptoms; he discontinued the 6-MP therapy when hemorrhages began or the leukocyte count fell to 1200-1500.

Tarantola (43) employed the combination of cortisone plus 6-MP to induce a fair clinical and hematologic response in a child, but the combination prednisone plus purine antagonist had no effect on another child, but Gelabert Sauchez (18) used the latter combination in the palliative therapy of an infant. Cap (6) induced a complete but brief remission in a five year old with delcortin plus 6-MP. Osamura (32) described a brief response in a nine year old boy with acute erythroleukemia who received prednisolone plus 6-MP, but who showed no improvement on mitomycin C; in contrast, a case of acute myeloid leukemia failed to respond to the steroid plus antipurine, but did show fair improvement on the antibiotic. Davis and Korst (12) secured a brief, partial response in a three year old boy who received prednisone plus 6-MP. Slooff (42) obtained almost complete remission in a boy placed on cortisone plus 6-MP, but the response was brief and the boy showed an enlarged kidney. McIlvanie and MacCarthy (27) noted that four children was acute leukemia developed hepatitis on prolonged use of prednisone plus 6-MP, which they

attributed to the latter drug. Rodenhäuser (34) attributed an eye hemorrhage in a child with acute paraleukoblastosis to the same combination of drugs.

Corticosteroids Plus Folic Acid Antagonists

The results of Hrodek and associates and Tuuteri *et al.* in combination chemotherapy of steroid hormones and folic acid antagonists have already been cited. Lightwood *et al.* (24) induced six partial remissions in 10 children with acute leukemia, following the use of adrenal steroids plus aminopterin; in 14 children administered the folic acid antagonist alone, they observed two complete and three partial responses; whereas, in 24 given 6-MP alone, they recorded three complete and five partial remissions. Louis *et al.* (26) described four remissions to 35 weeks in five children placed on steroids plus aminopterin; in two adults receiving steroids only, there was no response while, in three children on corticoids, there were complete remissions extending to 36 weeks. Sato (38) induced an average survival of 457 days with corticosteroids plus antifolic acids, which was twice the length of survival achieved with steroids plus 6-MP. Antonucci and Ramenghi (2) reported less response with prednisone plus aminopterin than with steroids plus 6-MP: they noted only one clinical and blood picture remission for 130 days in six children receiving the antifolic combination while, with the purine antagonist, they described four clinical and three hematologic remissions for an average survival of 316 days in five cases. Chaptal *et al.* (8, 9) observed complete clinical and hematologic remissions in two children for two and three months, following the use of cortisone plus aminopterin. Schaerer *et al.* (39) described an infant who had a complete remission but developed cirrhosis of the liver and multiple fractures after 20 months on prednisone plus folic acid antagonists. Palitzsch (33) developed a good remission in a child by administering cortisone plus amethopterin. Davis and Korst (12) noted no improvement in a boy after combination therapy with methylprednisolone plus methotrexate.

Corticosteroids Plus 6-Mercaptopurine Plus Folic Acid Antagonists

Zuelzer (49) reported on a 10 year study of 169 children with stem-cell leukemia: during the first five years (1950-54), the therapy of 76 cases was with corticoids, folic acid antagonists and 6-MP, but

with no uniform sequence; he tabulated 84.2 per cent complete and 11.9 per cent incomplete remissions; 93 children were treated during 1955-59 with a combination of prednisone plus 6-MP, followed by the antipurine alone for three months; then amethopterin was substituted for 6-MP for three months; the rotation of the two antimetabolites was continued until relapse when steroids were resumed in combination until remission was again achieved; this schedule resulted in 94.6 per cent complete and 2.2 per cent incomplete responses; the mean survival time of 1950-54 was 8.1 months, while that for 1955-59 was 13.0 months with 28 cases surviving 18 to 87 months, and one child was in good health seven years later. Hansen (19) treated 34 children with acute leukemia with adrenal steroids, 6-MP, and folic acid antagonists; he recorded 67 per cent remissions lasting to 21 months (average 11 months) with 50 per cent surviving for 15 months, and 10 per cent for 19 months. Draper and Fordham (13) tabulated the results of 25 years of management of children with acute leukemia: 23 children who received no therapy had an average survival of only two weeks; in 48 children given blood transfusions only, the average survival was nine weeks; in 26 given transfusions, steroids, 6-MP, and methotrexate in rotation, the average survival was 26 weeks. Aboul-Nasr (1) achieved three moderate remissions in five children treated with cortisone plus 6-MP plus aminopterin. Dubois-Ferriere and Kalaci (14) described a 10 months' remission in a patient with lymphoblastic leukemia who was given the combination prednisone plus 6-MP plus methotrexate. Vignetti (48) in a study of different cytostatic drugs on acute leukemia in childhood secured a remission for a year in one case administered cortisone, plus delta cortisone plus 6-MP plus amethopterin plus transfusions.

6-Mercaptopurine Plus Folic Acid Antagonists

Frei and eight associates (15) in 1958 published a comparative study of two regimens of combination chemotherapy in acute leukemia: the comparison of daily administration of methotrexate and daily 6-MP with the administration of methotrexate every third day and the same daily 6-MP dose showed no difference in frequency of remissions, duration of remissions, or toxicity in the two comparisons but, among those patients who obtained remission status, the duration of remissions and the survival rate was longer in the con-

tinuous group. All remissions of children were in the acute lymphocytic leukemia while, in adults, all responses were in acute myelocytic leukemia; 14 of 39 children, or 36 per cent, had complete or partial remissions; five of 26 adults, or 19 per cent, had remissions and these were of longer duration than in children. In 1959, Frei and Haurani (16) reported 50 per cent remissions in children given the combination mercaptopurine plus methotrexate, but only 5 per cent response in adults; when the drugs were given in sequence, the rate in children was 41 per cent. Olsson (31) obtained good remissions in five of six children administered methotrexate plus mercaptopurine. Shaw *et al.* (41) employed the combination, methotrexate plus 6-MP, in 21 children with acute leukemia who had the complication of increased intracranial pressure; the remissions were shorter than in those without this condition.

Discussion and Conclusions

The use of combination chemotherapy in the management of acute leukemia is a subject of controversy. Dr. G. Crile, Jr. expresses the opposition to this form of therapy in these words: "Combinations of alkylating agents are no more effective than is the use of the drugs separately. When two or more alkylating agents such as nitrogen mustard and thioTEPA are given, the total toxicity to the host is increased proportionately and the effect on the cancer cell is no more specific than if a single agent had been employed" (11). Dr. D. S. Martin (28), on the other hand, argues for the use of two or more drugs, because "a single neoplasm is composed of a diversity of malignant cell types. It is therefore possible that each cell type may require a different chemotherapy."

Tabulations from the present study in the results in childhood leukemia of the combination, corticosteroids plus 6-MP, show a larger synergistic effect than that reported recently with these two drugs for the management of acute leukemia in patients of all ages (36): calculations from investigations which record both the number of children treated and the number responding give a 71 per cent remission rate for the more than 200 patients, which is 11 per cent higher than that noted for all age groups. The combination of corticosteroids plus folic acid antagonists shows approximately the same remission rate for both childhood and the all-age group (37). Computations of the results in children who were administered the

three cytostatic drugs, corticoids, mercaptopurine, and folic acid antagonists, show a remission rate of 86 per cent for the 134 cases which could be evaluated. A number of investigators comment on the longer survivals in combination chemotherapy over those observed in single drug therapy, and there are few complaints of increased toxicity in the use of multiple drug therapy. Recognition, however, should be taken of the limited number of children treated in this study, and the different standards followed in determining remissions by the many investigators in widely separated medical centers.

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